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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/565,119	GERHARDT ET AL.
Examiner	Art Unit	
	Suchira Pande	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 09 August 2007.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 3,5-9 and 12 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 3,5-9 and 12 is/are rejected.

7) Claim(s) 3 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) Paper No(s)/Mail Date. _____ ..
3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date. _____ . 5) Notice of Informal Patent Application
6) Other: _____ .

DETAILED ACTION

Claim Status

1. Amendment filed on August 9, 2007 is acknowledged. Applicant has cancelled claims 1, 2, 4, 10 and 11. Claims 3 and 7 have been amended. New claim 12 has been added. Currently claims 3, 5-9 and 12 are pending and will be examined in this action.

Rejection of claims 10 and 11 under 112

2. Cancellation of claims 10 and 11 renders this rejection moot. Accordingly the 112 rejections of claims 10 and 11 are being withdrawn.

Response to Arguments re of claims under 102(b) rejection over Atten et al. as

evidenced by Ji et al.

3. Applicant's arguments, filed August 9, 2007, with respect to rejection of claims under 102(b) over Atten et al. as evidenced by Ji et al. have been fully considered and are persuasive. The previous 102 (b) rejection of claims 1-6 and 9-11 has been withdrawn.

4. Applicant has amended claim 3 to incorporate limitations of claim 4. Subject matter of both claims was taught by Atten et al. as evidenced by Ji et al. and properly rejected in previous office action. Applicant argues that no mention is made of ghrelin. Examiner has shown that prior art teaches the exact same gastric cell lines (RF-1 having ATCC number CRL-1864 and RF-48 having ATCC number CRL-1863) claimed in the instant application grown under the conditions claimed by applicant and these gastric cell lines are used to assess effect of different compounds on gene expression of these gastric cell lines. Therefore RF-1 and RF-48 cell lines will produce ghrelin when

they are grown in Leibovitz's L15 containing 10% (vol/vol) foetal bovine serum and 2 mM L-glutamine, and wherein the cell line is grown at a temperature of 37°C in the absence of CO₂. Moreover production of ghrelin is inherent property of the gastric cell lines (This is evidenced by Kojima et al. 1999 Nature vol. 402: pp 656-659 where identification of purified ghrelin ligand from stomach—(gastric tissue) is taught). Ji et al do teach use of cell lines in the large scale drug screening (see page 6549 par. 3 and also see page 6551 par. 1). Since Kojima et al. and Ji et al are not directly cited by Atten et al. Therefore the 102(b) rejection over Atten et al. as evidenced by Ji et al. is being changed to a 103(a) rejection over Atten et al. in view of Ji et al and further in view of Kojima et al.

5. Insofar applicant's arguments apply to previously cited secondary references used along with 102 (a) rejection for make 103(a) rejections, they are not persuasive. The secondary references in view of the newly cited references that teach the base amended claim are still valid and are being maintained.

Claim Objections

6. Amended claim 3 is objected to because of the following informalities: Last line of claim contains a spelling error "ghreling" should be spelt "ghrelin". Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 5-9, 12 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The first active step recited in the claim is to grow the claimed cell lines RF-1 and RF-48 in suitable medium. The final part of claim recites--- wherein the effect of a test compound on ghrelin expression and/or secretion is screened. The claim as recited fails to provide guidance to one of ordinary skill what exactly should be done to practice the invention. The omitted steps are: the intermediary steps that must follow after the cells are grown in suitable media so that final desired end result namely -- effect of a test compound on ghrelin expression and/or secretion is screened" is achieved. In other words the active intermediary steps are missing in the claim 3 as currently recited.

Regarding claim 12, the claim as recited describes intended use of the claim. The claim as recited is totally lacking in recitation of active steps that must be followed to achieve the intended desired end result, namely, developing drugs or functional ingredients for food products that modulate feelings of satiety or appetite in humans or animals.

Claim interpretation

8. Regarding claim 3, for purposes of applying art, in view of the above identified 112 issues, Examiner is interpreting that any method that is known in the art to screen test compounds will be applicable to claim 3 as currently recited.

Regarding claim 12, in absence of active method steps the teaching from prior art that ghrelin is produced by stomach and acts on various parts of brain is being

broadly interpreted to mean that ghrelin's action on brain signals the feelings of satiety or appetite in humans or animals.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 3, 5- 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atten et al. (2001) Biochemical Pharmacology 62: 1423-1432 in view of Ji et al. (2002) Oncogene 21:6549-6556 and further in view of Kojima et al (1999) Nature 402:pp 656-659.

Regarding claim 3, Atten et al. teach : wherein the cell line is selected from RF-1 having ATCC number CRL-1864 and RF-48 having ATCC number CRL-1863 (see page

1424 section 2.2 where RF-1 having ATCC number CRL-1864 and RF-48 having ATCC number CRL-1863 are taught).

Regarding claim 3, Atten et al. do not explicitly teach the cell line RF-1 and RF-48 is a suitable model for the study of the (regulation of) expression, synthesis and/or secretion of ghrelin.

Regarding claim 3, Ji et al. teach use of teach the cell line RF-1 and RF-48 is a suitable model for the study of the (regulation of) expression, synthesis (see title and page 6556 where Ji et al. teach use of these cell lines submitted to ATCC as models). Ji et al. teach comprehensive analysis of gene expression profiles in human gastric cancer cell lines (see abstract). On page 6552, par. 2 Ji et al. teaches gastric carcinoma cell lines (RF1 and RF48).

Regarding claim 3, neither Atten et al. nor Ji et al. explicitly state that RF-1 and RF-48 is a cell line capable of producing ghrelin.

Regarding claim 3, Kojima et al. teach ghrelin is a growth-hormone-releasing acylated peptide from stomach. (see Kojima et al. 1999 where identification of purified ghrelin ligand from stomach (gastric tissue) is taught). RF-1 as a cell line derived from gastric adenocarcinoma. Kojima et al teaches one of ordinary skill in the art that ghrelin is a growth-hormone-releasing acylated peptide from stomach. Since both the cell lines taught RF-1 and RF-48 are gastric cell lines hence they are capable of producing ghrelin is an inherent property of these two cell lines. It is obviously clear to one of ordinary skill in the art that cells have to be grown under appropriate conditions if one wants to examine expression of a specific marker. If one was interested in studying

expression of ghrelin from a cell line derived from a gastric adenocarcinoma and capable of producing ghrelin. The one would grow it in a suitable medium. The suitable growth medium and conditions required are taught by Atten et al. (see page 1424 section 2.2 where media and conditions required to grow RF-1 cells is described).

Moreover since Ji et al. teach gene expression profiling of several gastric cell lines including RF1 and RF48, it is inherent that the method taught by them is capable of assessing the (regulation of) expression, synthesis and/or secretion of ghrelin (which as indicated above is an inherent property of the two cell lines taught). In addition Ji et al. teach large -scale drug (test compounds) screening using cell lines (see page 6549 par. 3). By these combined teachings, Ji et al. teach a test compound when screened using the above cell lines will provide information about the effect of these compounds on ghrelin expression and /or secretion. Thus allowing for a method to screen the compounds for their effect on ghrelin expression and /or secretion.

Thus Atten et al. in view of Ji et al. and Kojima et al. teach a method for assessing the (regulation of) expression, synthesis and /or secretion of ghrelin, wherein a cell line derived from a gastric adenocarcinoma and capable of producing ghrelin when grown in a suitable medium, is grown in such medium wherein the cell line is selected from RF-1 having ATCC number CRL-1864 and RF-48 having ATCC number CRL-1863 and wherein the effect of a test compound on ghrelin expression and /or secretion is screened.

Regarding claim 5, Atten et al. teach wherein the medium is Leibovitz's L15 containing 10% (vol/vol) foetal bovine serum and 2 mM L-glutamine, and wherein the

cell line is grown at a temperature of 37.degree. C. in the absence of CO₂ (see page 1424 section 2.2.). Atten et al. states the Leibovitz's media taught is supplemented with non-essential amino acids and do not explicitly recite using 2 mM L-glutamine.

Glutamine is classified as a non-essential amino acid (see report in Le Magazine published on September 1999 by Greenwell). One of ordinary skill in the art knows that MEM media routinely used for cell culture contains 292 mg/l L-glutamine. Using the formula weight provided by Sigma Aldrich as 146.14 for L-glutamine one can calculate that 292.28 mg of L-glutamine/l media would result in 2 mM L-glutamine. So its clear that one of ordinary skill would add the appropriate amount of L-glutamine as a non-essential amino acid to the media taught by Atten et al. Thus all elements of claim 5 are taught by Atten et al.

Regarding claim 6, Atten et al. teach cell culture conditions for the two cell lines taught. They do not explicitly state that, wherein the medium is changed at least every 4 days. However this is a fact that is well known to one of ordinary skill in the art of mammalian tissue cell culture (see Basic Techniques for Mammalian cell tissue culture unit 1.1.2 where Mary C. Phelan describes in step 7. If necessary, feed subconfluent cultures after 3 or 4 days by removing old medium and adding fresh medium.)

Regarding claim 9, Atten et al. teach wherein the cell line is exposed to a variety of test compounds (see title and abstract where exposure to test compound Resveratol (potential chemo preventive candidate against gastric cancer is taught, see page 1430 last par. last line.). Ji et al. teach that variety of test compounds is indeed routinely used

to study responsiveness of each cell line (see Ji et al. page 6551. par. 1). This teaching inherently requires that cell line under question be exposed to those test compounds).

Regarding claim 12, Atten et al. in view of Ji et al. and Kojima et al. teach method of claim 3. Further regarding claim 12, Kojima et al. state " Taken together with the fact that ghrelin, when injected intravenously, induces GH (growth hormone) release, it is highly likely that this molecule (ghrelin) is produced in and secreted from the stomach, circulating in the blood stream to act on pituitary" (see page 659 par. 1). They further state "these results suggest that ghrelin in the arcuate nucleus may act on the hypothalamus or be transported to anterior pituitary' (see page 659 par. 2). Finally they state :"Thus, the occurrence of ghrelin in both stomach and hypothalamus will give new dimension to the regulation of GH release. ----Ghrelin may thus have multifaceted roles in, for example the cardiovascular system and metabolism" (see page 659 par. 3). Thus Kojima et al. teach to one or ordinary skill in the art that ghrelin is produced by stomach into blood and its carried to brain where it acts on various parts of brain (arcuate nucleus/ hypothalamus/anterior pituitary) that are control feelings of satiety or appetite in humans or animals.

It would have been *prima facie* obvious to one of ordinary skill in the art to practice the method of Ji et al. and Kojima et al. in the method of Atten et al. at the time the invention was made. The motivation to do so is provided to one of ordinary skill by the art itself. Kojima et al. teaches to one or ordinary skill in the art that ghrelin is produced by stomach into blood and its carried to brain where it acts on various parts of brain (arcuate nucleus/ hypothalamus/anterior pituitary) that are control feelings of

satiety or appetite in humans or animals. Ji et al. teaches use of gastric cell lines RF-1 and RF-48 to screen a variety of compounds. If one was interested in screening for compounds that affect ghrelin production which in turn goes by blood to effect the appropriate part of brain to effect feelings of satiety or appetite in humans or animals, then The adenocarcinoma cell lines RF-1 and RF-48 would be obvious candidates in view of teachings of Kojima et al. Atten et al. provide the detailed step by step protocol of how to grow these cell lines. Thus by using the combination of the above methods of ordinary skill in the art would be able to screen for compounds that affect ghrelin production using these cell lines taught to them by prior art.

12. Claim 7 rejected under 35 U.S.C. 103(a) as being unpatentable over Atten et al. (2001) Biochemical Pharmacology 62: 1423-1432 in view of Ji et al. (2002) Oncogene 21:6549-6556 and further in view of Kojima et al (1999) Nature 402:pp 656-659 as applied to claim 3 above, and further in view of Chopin et al. (2002) WO 02/090387 A1 published 14 November 2002.

Regarding claim 7, Atten et al; Ji et al. and Kojima et al. teach method according to claim 3.

Regarding claim 7, Atten et al; Ji et al. and Kojima et al. do not explicitly spell out wherein the cell line is plated and grown in a culture plate after achieving cell confluence, wherein the plate is stored under the same incubation conditions as those used for growing the cell line (since Atten et. al. teaches media and cell culture conditions used for the cell lines claimed in the present invention it is obvious that above

conditions specified are inherently obvious to one of ordinary skill), and wherein ghrelin production is measured using an immunoassay kit.

Regarding claim 7, Chopin et al. teach wherein the cell line is plated and grown in a culture plate after achieving cell confluence (see page 25, lines 24-26 where culture of cells in 96 well plates for 3 days at 37°C is taught), wherein the plate is stored under the same incubation conditions as those used for growing the cell line (for the purposes of detecting ghrelin which is a small amino acid peptide it is obvious to one of ordinary skill in the art that the culture plate needs to be stored under conditions where the ghrelin peptide will not be destroyed. Culturing the cells in the media containing Liebovitz's media under the conditions specified in claims 1, 3 and 5 above results in production of ghrelin. Therefore it is inherently obvious to one of ordinary skill that storing the plates containing the produced ghrelin under the same incubation conditions as those used for growing the cell line will not destroy the ghrelin produced.

and wherein ghrelin production is measured using an immunoassay kit (Chopin et al. teach use of three different assays using antibodies raised against ghrelin (see page 24, line 23-25. Therefore by teaching Western blots, immunohistochemistry and ELISA assay for ghrelin using anti-ghrelin antibodies raised against whole human ghrelin peptide, Chopin et al. teach immunoassays that use anti-ghrelin antibodies. Thus Chopin et al. inherently teach all the components required to perform these immunoassays that would be packaged in a kit.

It would have been *prima facie* obvious to one of ordinary skill to practice the method of Chopin et al. in the method of Atten et al; Ji et al. and Kojima et al. to

measure the ghrelin peptide production by these cells at the time the invention was made. The motivation to do so is provided by Chopin et al. who teach availability of antibodies raised against ghrelin thus providing the reagent required by one of ordinary skill in the art to perform immunoassays to detect ghrelin.

13. Claims 7 and 8 rejected under 35 U.S.C. 103(a) as being unpatentable over Atten et al. (2001) Biochemical Pharmacology 62: 1423-1432 in view of Ji et al. (2002) Oncogene 21:6549-6556 and further in view of Kojima et al (1999) Nature 402:pp 656-659 as applied to claim 3 above, and further in view of Korbontis et al. (2000) The Journal of Clinical Endocrinology & Metabolism vol. 86: pp 881-887.

Regarding claim 8, Atten et al; Ji et al. and Kojima et al. teach method according to claim 3.

Regarding claim 8, Atten et al; Ji et al. and Kojima et al., do not explicitly teach wherein the cell line is used to study ghrelin gene expression, preferably by means of quantitative RT-PCR.

Regarding claim 8, Korbontis et al. teach wherein the tumor cells are used to study ghrelin gene expression (see title and abstract), preferably by means of quantitative RT-PCR (see page 883 section Quantitative RT-PCR).

Regarding claim 7, Korbontis et al. teach Ghrelin RIA that is capable of detecting both octanoylated (active) and non octanoylated (inactive) forms of ghrelin peptide. Thus by teaching the two separate polyclonal antibodies of ghrelin that are useful for detecting the above two forms of ghrelin peptide and their use in RIA, Korbontis et al.

teach immunoassay that can be used monitor ghrelin production. By teaching the immunoassay, Korbontis et al. obviously teach all the components of the kit required to detect ghrelin using the immunoassay.

It would have been *prima facie* obvious to one of ordinary skill in the art to practice the method of Korbontis et al. in the method of Atten et al as evidenced by Ji et al. at the time the invention was made. The motivation to do so is provided to one of ordinary skill by the fact that Korbontis et al. use the Quantitative RT-PCR method to study expression of ghrelin and ghrelin RIA.

They used primary tumor tissues expressing ghrelin as their starting material. Atten et al. as evidenced by Ji et al. teach study of gene expression in gastric adenocarcinoma cell line using micro arrays. Atten et al; Ji et al. and Kojima et al. have shown (see *supra*) that two of the gastric adenocarcinoma cell lines (RF1 and RF48) produce ghrelin. Given the above fact pattern it is obvious to one of ordinary skill in the art that use of Quantitative RT-PCR method of Korbontis et al. will be able to detect ghrelin gene expression in the cell lines claimed. The advantages and ease of working with established cell lines (RF1 and RF48) available through ATCC (ATCC #CRL-1864 and ATCC # CRL-1863) vs. primary tumors tissue are well known to one of ordinary skill well versed in mammalian tissue culture.

Further use of method of Korbontis et al. allows one of ordinary skill to be able to monitor both the gene expression and actual production of ghrelin peptide. Thus enabling one to arrive at comprehensive picture of the various levels of controls

(transcriptional and translational) that are operational under given experimental conditions.

Conclusion

14. All claims 3, 5-9 and 12 are rejected.
15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suchira Pande whose telephone number is 571-272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER

Chalot